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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/534,353 | 05/09/2005 | Jong-Soo Woo | Q87237 | 4817 |

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| EXAMINER | |
|---|---|
| PALENIK, JEFFREY T | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | |

| NOTIFICATION DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/534,353 | WOO ET AL. | |
| | Examiner | Art Unit | |
| | JEFFREY PALENIK | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 March 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *11-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### STATUS OF THE APPLICATION

Receipt is acknowledged of Applicants' Request for Continued Examination (RCE) and Remarks, filed 2 March 2011, in the matter of Application N° 10/534,353. Said The Examiner further acknowledges the following:

Claims 1-13 are pending, where claims 11-13 remain withdrawn from consideration.

No claims have been added, amended or cancelled.

No new matter has been added.

Thus, claims 1-10 continue to represent all claims currently under consideration.

### INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been filed for consideration.

### MAINTAINED REJECTIONS

The following rejections are maintained from the previous Office Correspondence dated 2 March 2011 since the art which was previously cited continues to read on the amended/newly cited limitations.

### CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham **v.** John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al. (US Pre-Grant Publication 2003/0064097) in combination with Kawamura et al. (US Pre-Grant Publication 2004/0219208).**

The instant claims remain drawn to a method for preparing a paclitaxel solid dispersion by a supercritical fluid process as discussed in the Office Action, mailed 21 March 2008. The process comprises dissolving a mixture of paclitaxel and additive in a mixed organic solvent. The solvent is next mixed via spraying with a supercritical fluid; the contact of the two solutions resulting in the formation of paclitaxel/additive particles. Any organic solvent remaining on the

particles is washed away using additional supercritical fluid. Lastly, the remaining particles are collected. The instantly amended claim 5 is interpreted by the Examiner as reciting a compositional limitation to claim 1 wherein the hydrophilic polymer (e.g., additive) is present in the solution mixture ranging from 1-75% (w/w) prior to the addition of the supercritical fluid.

Patel et al. teach methods for preparing multiparticulate compositions using processes which comprise applying an encapsulation coat onto a substrate (e.g., spray coating and nanoencapsulation) as well as collection of the ensuing particles ¶[0223]. Preparation of the encapsulation coating solution is taught as solubilizing or suspending a composition in a mixture comprising an organic solvent and a supercritical fluid, and which can further comprise additives. Paragraph [0039] teaches paclitaxel as one of the most preferred hydrophobic active ingredients used in the encapsulation coating composition. Paragraph [0257] specifically teaches that multiple organic solvents may be combined as the organic solvent of the coating solutions. Additives are, again, taught as being part of the coating solution composition. Removal of the dispersing medium (e.g.,. the organic solvent of the coating solution) is taught as occurring at the end of the coating process and in the form of drying process (e.g.,. heating, vacuuming, etc.). Recovery of the resulting particles may be accomplished by forming pellets, granules, or spheres, for example ¶[0228].

Patel et al. further teach additives which include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and polyvinyl pyrrolidone (PVP) ¶[0166]. PVP, in particular, is taught as both a binder ¶[0166] and a disintegrant ¶[0174]. Where the coating composition is applied to the particles as a delayed release enteric coating, acrylic polymer additives such as methacrylic acid copolymers as well as other polymers of the Eudragit series

(e.g.,. E, L, S, RL, and RS) are preferably used ¶¶[0190], [0191] and [0202]. The methods discussed at ¶[0224] employ organic solvents which are further defined at ¶[0257] as mixtures of different solvents such as methanol, ethanol, isopropanol, dichloromethane, and ethyl acetate.

Patel et al. do not expressly teach removal (e.g.,. displacement) of the mixed organic solvent portion of the dispersing medium by washing the coated particles with additional supercritical fluid, but do additionally teach that modifications to the coating process, such as the drying processes, are well known in the art ¶[0226]. Patel et al. also do not expressly teach Applicants' instantly claimed polymer/active weight ratio, percent range of the hydrophilic polymer or the weight ratio of the two organic solvents mixed.

Kawamura et al. teach a process for preparing a sustained-release preparation comprising injectable microcapsules or microspheres ¶¶[0225] and [0226] which comprises an AII antagonist and an anticancer drug (Abstract; claim 1). Paclitaxel is specifically taught as a plant-derived anticancer agent ¶[0154] which may be employed in the formulation. One such process for preparing said particles or spheres is described in ¶[0259] wherein a compound comprising an AII antagonist and optionally water are added to a solution of additive (e.g.,. biodegradable polymer) in an organic solvent. Paragraph [0263] teaches different ranges of ratios of the organic solvents (i.e. ratio of dichloromethane to ethanol or methanol). Biodegradable polymers such as PVP are taught as emulsifier additives which may be present at preferable concentration ranging from about 0.01-10% by weight ¶¶[0262] and [0265]. Said solution is then finely dispersible by homogenization or by ultrasound over said particles. The organic solvent used is expressly taught as comprising a mixture of different organic-based solvents ¶[0260] as well as

an additive ¶[0261] and/or an emulsifier ¶[0265]. Paragraph [0276] teaches methods for removing water and organic solvents from the coated particles which include evaporation and/or vacuuming. A more specific method for removal of water and organic solvent is expressly taught as being performed using a supercritical fluid in a high pressure gas state ¶[0283]. Collection of the resulting microcapsule particles by centrifugation or filtration is taught in ¶[0277].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a nano-scale paclitaxel solid dispersion (e.g., suspension) by contacting a paclitaxel/additive/mixed alcohol solvent solution with a supercritical fluid, displacing said alcohol solvent with supercritical fluid and recover the resulting particles, as taught and suggested by the combined teachings of Patel et al. and Kawamura et al.

One of ordinary skill in the art would have been motivated to do this because Patel et al. provides teachings for every aspect of the instantly claimed method except where the organic solvent is removed using supercritical fluid. Patel et al. do teach that at the end of the particle coating process, the residual dispersing medium, which includes the mixed organic solvent, can be further removed to a desirable level utilizing appropriate drying processes such as vacuum evaporation, freeze drying and heating ¶[0224]. The ordinarily skilled artisan, in view of this teaching and ¶[0226], would have been highly motivated to substitute a gas-propelled process for a suction-based process of evaporating organic solvents, such as the solvent removal method taught by ¶[0283] of Kawamura et al., particularly since said removal method explicitly teaches using a supercritical fluid in a high pressure gas-state to remove organic solvents (i.e., mixed ethanol and methanol). Furthermore, while Patel et al. do not expressly teach the claimed order

of the addition of components of the instantly claimed method, it would have been prima facie obvious to a person of ordinary skill in the art that there is no patentable distinction between Applicants' method and the methods taught in the prior art. The selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results. In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) Selection of any order of mixing ingredients is also held to be prima facie obvious. In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (see MPEP 2144.04 (IV)(C.))

Neither of the references explicitly teach polymer/active weight ratio, percent range of the hydrophilic polymer or the weight ratio of the two organic solvents mixed, as claimed by Applicants. The amounts and ratios of specific ingredients in a composition are clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize as is format of oral dosage (i.e., tablet versus capsule). Optimization of parameters, such as the size of granulated particles, is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amounts and ratios of each ingredient to add in order to best achieve the desired method as cited in the instant claims. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amounts would have been obvious at the time of Applicant's invention.

Given the mixture process steps taught by Patel et al. as well as the modified, supercritical fluid based, organic solvent evaporation step suggested by Patel et al. and taught by Kawamura et al., and since both inventions are directed towards methods for solubilizing

insoluble drugs such as paclitaxel in small scale, particulate-based drug delivery compositions, it follows that the combined teachings would have afforded the ordinarily skilled artisan a reasonably high expectation of success for producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the combined references, especially in the absence of evidence to the contrary.

**Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Patel et al. and Kawamura et al. as set forth above with respect to claim 1 in combination with Nielsen et al. (USPN 5,716,558).**

Neither Patel et al. nor Kawamura et al. teach the temperature or pressure application parameters for the supercritical fluid as set forth by Applicants in claim 10.

Nielsen et al. teach methods for spraying liquid compositions by using compressed fluids such as carbon dioxide, to form solid particulates and coating powders which may be produced with narrow particle size distributions (Abstract). Nielsen et al. further teach that compressed carbon dioxide fluid may be sprayed at a temperature of 60°C and a pressure of 1600 pounds/sq. inch (1 bar/14.5 psi; http://onlineconversion.com/pressure.htm) or about 110.3 bar (col. 13, lines 19-26).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to have sprayed a supercritical fluid (e.g., carbon dioxide) using Applicants' instantly claimed physical parameters in view of Nielsen's teaching that application

of a supercritical fluid to a liquid water-borne polymeric composition comprising a mixed organic solvent produced a dry, collectable powder (Example 9).

## RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 1-9 under 35 USC 103(a) as being unpatentable over the combined teachings of Patel et al. and Kawamura et al., as well as with regard to the rejection of claim 10 under 35 USC 103(a) as being unpatentable over the combined teachings of Patel et al., Kawamura et al. and Nielsen et al. have been fully considered but they are not persuasive.

Applicants allege that the combined teachings of Patel et al., Kawamura et al. and Nielsen et al. fail to teach all limitations of the independent claim and proceed to provide dissolution testing results as evidence thereto. The evidence provided is directly compared to the results of Examples 2 and 3 of the Patel reference alone. Applicants further argue that the amounts of surfactant (e.g., Myrj 52) employed in the compositions of Patel are about ten times higher and are part of the reason that dissolution is improved.

In response, the Examiner initially points out that the Nielsen et al. reference is not relied upon until addressing the limitations of claim 10. Similarly, concerning the forthcoming responses, the rejection of claim 1 is not based solely on the teachings of Patel et al.

Thus, in response to Applicants' arguments against the references individually (e.g., Patel alone), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Next, in response to Applicants' argument that the references fail to show certain features of Applicants' invention, it is noted that the features upon which Applicant relies (i.e., an amount of surfactant) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, the Examiner notes that Applicants' second claim recites that the additive is either a hydrophilic polymer or a surfactant [emphases added]. The remaining dependent limitations directed to the additive are further limited as a hydrophilic polymer and not a surfactant (see e.g., claims 3-5).

Lastly, Applicants' Dissolution Testing discussion and results have been carefully considered. Respectfully, these remarks and showings are not sufficient in overcoming the rejections of record. The primary reason that the showing is unpersuasive is due to the materials compared in the study (see **ii**, middle of page 6). Applicants' study pits the compositions of the instant Examples 1 and 22 against a control of pure bulk (i.e., untreated) paclitaxel. The table on the top of page seven of the Remarks depicts the improved solubility (e.g., about 3,000 times better) of Applicants' instant invention over plain, untreated paclitaxel. Essentially, Applicants demonstrate that paclitaxel has poor solubility in aqueous systems, a fact which is very well established, and that their method improves solubility. Nowhere does Applicants' comparative testing weigh the product of the instant method against that which is made by the method in the art. To be clear, the Examiner is not disagreeing with the fact that Applicants' instant method improves/enhances paclitaxel solubility. The position the Examiner takes is that Applicants have not provided a sufficient showing which distinguishes over the method disclosed by the art of

record. In this case, a prima facie case of obviousness has been made that the art teaches the improved solubilization of insoluble drugs such as paclitaxel.

Applicants' argue these results in contrast to Examples 2 and 3 in Patel et al., but as discussed before, this is not considered to be persuasive. Applicants previously acknowledged on the record that the aforementioned Patel et al. Examples respectively depict improving the solubilities of glyburide and progesterone active ingredients. Applicants then appear to use this as a direct comparison to the formulation achieved in the instant invention.

The Examiner respectfully maintains that such a comparison is not commensurate in scope with the instant invention as different active ingredients will each possess their own distinct solubilities, treated or untreated. Further, as discussed above, the Patel et al. reference alone provides sufficient direction so as to teach and suggest to the artisan of ordinary skill that paclitaxel and an additive may be mixed with organic solvent(s) in order to form particles upon spray-combination with a supercritical fluid. While the Examiner acknowledges that the Patel et al. reference does not disclose specifically disclose an example(s) incorporating paclitaxel, it is maintained that such combinations are taught and are suggested, particularly since "[a] reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989) [see MPEP §2123(I)]. That being said, each of the different formulations would have been prima facie obvious to a person of ordinary skill in the art, absent a clear showing of evidence to the contrary.

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore **maintained**.

All claims under consideration remain rejected; no claims are allowed.

## CONCLUSION

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

## CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966.

The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner
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